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DISEASES OF THE NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

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DISEASES of the NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Emotional Aspects of the Narcolepsies

(With Report of a Case of Sleep Paralysis)

THEODOR BONSTEDT, M.D.
Ann Arbor, Michigan

The term narcolepsy was first used by Gelinau in 1880 although Jelliffe (according to Wagner[44]) was able to trace the description of this condition to the Greco-Roman medicine. Gelinau originally defined narcolepsy as "a new species of neurosis" exhibiting attacks of involuntary diurnal sleep,[1] and the syndrome retained this name until today.

In 1902 Loewenfeld[35] described attacks of transitory paralysis with tonelessness after sudden emotion as belonging to the narcoleptic syndrome. For these the name of cataplexy was coined by Henneberg. While these two components of the narcoleptic-cataplectic syndrome occur simultaneously fairly frequently, the other conditions today commonly designated as narcolepsies[46] are not as often met with in narcoleptic patients and may be diagnosed in otherwise healthy people. Here belongs the sleep paralysis first described by Mitchell in 1876 and divided into the pre- and post-dormitial variety, in which the paralysis resembling cataplexy occurs respectively on falling asleep and/or on awakening from sleep.

All these conditions (particularly sleep paralysis) may be associated with fearful and vivid half-waking dreams called sleep hallucinosis, and in several recorded cases sleep hallucinosis had gradually led to a paranoid psychotic state.[6] Brock and Wiesel[6] include also somnambulism and somniloquism under the heading of the narcolepsies and compile in such way the following table taken from their paper:

Today there is general agreement with Wilson[47] that narcolepsy is a syndrome with varied etiology yet with the same physiological mechanism and not a separate disease entity as it was formerly believed.[1]

Studies of cases of narcolepsy recorded in the literature lead us to believe that practically any combination and chronological succession of the above constituents have been encountered in particular cases. Patients are predominantly (70%-80%) males, with the symptoms starting mostly at or after puberty and then persisting indefinitely with variable frequency but without any influence on the life expectancy of the individual. Grinker[17] and Wilson[47] mention as possible etiological factors trauma, endocrine dysfunction, epilepsy, infection (encephalitis), circulatory disturbances, tumors of the area around the third ventricle, and the remaining cases of narcolepsy, in which no organic etiology can be elucidated, are called "idiopathic." However, Grinker mentions a psychogenic etiology as a separate factor, whereas most other authors—if they ever recognize psychic causation—would suspect it under the heading of the "idiopathic" narcolepsy. This designation is usually meant to express our lack of knowledge of the actual etiology in question. It is this latter group of the narcolepsies which we shall evaluate in this paper in an attempt to establish how much we do know today about the significance of the psychogenic component in this fascinating and vague disease syndrome.

Constituents of Narcoleptic-Cataplectic Syndrome	Stimulus	Type of Sleep Activity: Mental aspects (stupor, etc.)	Physical aspects tonelessness, etc.)
1. Narcolepsy (diurnal sleep attacks)	? sometimes emotional	Present	Present (complete or partial)
2. Cataplexy	Emotion	Absent	Present
3. Sleep paralysis, pre- or post-dormitial	(?) (Emotion arising in dream)	Partly Present	Present
4. Somnambulism	?	Present	Absent
5. Somniloquism	?	Part. Present	Present
6. Sleep hallucinosis	?	Part. Present	Present
7. Paranoid psychotic state			

In a typical case of a narcoleptic patient a certain degree of somnolence and physical and mental fatigue is characteristic in the period between spells.[27,28] The spells may occur while the patient is comfortably relaxing in a chair but they may also occur in any life situation however exciting it may be—while driving a car,[27] under bombardment and on sentry duty,[24] at the dinner table or while walking on the street. Patients may remain asleep for a few seconds or several minutes and there may be as many as five or ten spells a day. Only occasionally can there be elicited an emotion preceding the spell—for instance, conscious anger, despair or fear.[24,28] Their sleep then usually cannot be distinguished from physiological sleep—not even by EEG.[14] Yet it has been noticed that their nocturnal sleep is as a rule restless and shallow.[16] In cataplexy, the precipitating emotion is much more constant and obvious, as when the person falls to the ground, paralyzed but conscious, in a moment of hearty laughter, or while raising his hand to whip his child, or while becoming angry because of another person's aggressive remarks, when surprised by something, however insignificant it may appear.[32] Wilson examined one such patient during an attack of cataplexy and found tonelessness, abolished patellar reflexes, and positive Babinski.[46]

Sleep paralysis appears to have all the features of the cataplexy except that it occurs on dozing off to sleep (between the stage of muscular relaxation and the stage of unconsciousness) or on awakening, and the patients are usually unable to recall the precipitating dreamy thought. They regain motor power as soon as they are touched or shaken. They frequently have vivid hypnagogic hallucinations (sleep hallucinosis) which as a rule are frightening and patients continue to be frightened thereafter even though they are aware of the unrealness of the experiences. Somnambulism and somniloquism seem to represent a direct counterpart to the cataplexy and sleep paralysis since in them the conscious part of the mind is asleep but the motor centers are not.

The problem of differential diagnosis does not usually present too great difficulties. It has been long suspected that the mechanism of production of the narcolepsies could be similar to that of the epilepsies. Gowers and Goldflam reported cases in which epilepsy and narcolepsy were co-existing in the same patient or succeeding each other in time, but the majority of narcoleptics do not belong to the hereditary-biological cycle of the epilepsies.[16] Although lack of twitchings and the ability to continue normal activity immediately after the spell permit an easy diagnosis of narcolepsy, the controversy about the relationship to the epilepsy has not been solved until recently.[39] While Aird, Gordon and Gregg[2] see an analogy to the psychomotor states with their limited integration and reported success with administration of Phenuron, and while Cohn[8] and Cruvant[39] found epileptic waking EEG patterns in their narcoleptic patients, other investigators arrive at differing conclusions regarding the waking EEG pattern of the narcoleptics. Dynes and Finley[14] found abnormal waking EEG patterns only in five out of 22 narcoleptics with no uniformity of the abnormal findings. Since those five patients also showed neurological signs and symptoms, the investigators concluded that they belonged to the symptomatic (organically caused) variety of narcolepsy. A differential diagnosis may also have to be made

against hyperinsulinism, pyknolepsy of childhood,[1] familial periodic paralysis,[16,34] and conversion hysteria. This latter presents another controversial point in the studies on narcolepsy.

The early writers on the subject[1,23,44,46] did not pay much attention to the emotional life and personality structure of the narcoleptics; Wilson[47] points out that catalepsy as observed in schizophrenia and hysteria may also occasionally be observed in the narcolepsy since it represents an intermediary stage between narcolepsy and cataplexy with muscle tonus being present. Some authors declare that hysteria cannot be diagnosed where other marks of the "hysterical personality" are absent,[4] while others flatly state that we have to deal here with a special type of hysteria[9,37,42], even though the narcoleptic patients are less difficult to arouse than hysterics, the spells are more generalized and always connected with sleep.[43]

Our understanding of the pathogenesis of narcolepsy has been developing along several lines of thought, and always in connection with a particular theory of the physiological sleep mechanism. It seems obvious that no adequate insight into the problems of narcolapsy can be gained until our knowledge about the function of sleep in general becomes more complete.

The oldest theory is that of a regulatory sleep center, usually located in the hypothalamus or around the third ventricle, which regulates the time limits of sleep and which in some way would be incapacitated in the narcolepsy even though the organic lesion in question may be thought of in terms of only chemical changes. Brock and Wiesel[6] point out the resemblance of the narcolepsy to the uncinate fit dreamy states and see as the common feature in both conditions the fact that only a part of the cortex (and consciousness) is active. Weitzner[45] used successfully a series of insulin injections in two caes of sleep paralysis and he assumes that the ACTH released in the body "increases the power of the hypothalamus to regulate sleep."

Recent advances in our knowledge of the diencephalon and its connections with the ascending reticular activating system of the midbrain, and the reticular inhibitory system, have produced some modification in the sleep center theory of the narcolepsy with introduction of the emotional component: Aird, Gordon and Gregg[2] explain the postdormitial sleep paralysis in the following way: an emotion in dream stimulates, i.e. awakens, patient's substrate of consciousness but at the same time it stimulates the reticular bulbar inhibitory system producing motor paralysis. Same emotion in waking state would produce cataplexy and a concomitant state of heightened consciousness. This would explain why dexedrine which would stimulate among others the reticular inhibitory system, does not help in cataplexy whereas it does improve the narcoleptic spells. The action of Phenurone in cataplexy would be that of inhibiting the reticular inhibitory system. The whole narcoleptic syndrome is thus understood as "a paroxysmal dysfunction of the hypothalamus, the subthalamic nuclei and their neurophysiological association tracts and centers."

Benedette[4] in his very recent paper takes a different approach although still within the frame of the organic reference. After noting that thus far out of approximately 200 dissertations on narcolepsy, only 20 touched upon the psychopathological side of the problem and recognized the connection with the personality structure, he states that the endocrinological part of the problem did not receive due attention until recently. Sleep is only one of the autonomic functions governed by the hypothalamus[11] which is in general the motor of emotion for its bodily expression. We know that local physiochemical disturbances in the hypothalamus as observed in acromegaly, Cushing's and Addison's disease will usually produce a "pituitary personality" characterized by apathy, retardation, indifference, often basic and reckless euphoria with affective lability. Tracing these features as somatic diencephalon signs in the literature on the narcolepsies Benedette concludes that the narcolepsy also is a "brain stem endocrine psychosyndrome" and as such cannot be explained on a psychogenic basis but does produce psychic symptoms.

Some writers view narcolepsy as a regression to a more primitive physiological level

as far as reflex function and adaptation to life are concerned. Brock and Wiesel[6] feel that narcolepsy corresponds to the primitive polyphasic sleep rhythm seen in lower animals and infants, in so far as the elements of normal sleep (tonelessness, unconsciousness and dreams) are excessive and dissociated from each other[16] forming parts of the narcolepsies, and these parts can be in their embryonic form encountered in normal people, e.g.: our relaxation in laughing, stiffness in grief, weakness while hearing sudden bad news. Along same lines Murphy[36] views narcolepsy as "a release phenomenon . . . produced by the diminution of the cortical activity either by physical damage to the cortical tracts or by their inhibition." Rosenthal[38] and Wilson[46] compare cataplexy to the reflex of imitating a dead body as it occurs in the animal world in times of a deadly fear.

As could be expected, Pavlov's theory of sleep as a widespread irradiated cortical inhibition was also utilized for explaining the nature of the narcolepsies. Levin[22,33] in a series of articles propounds the idea that an attack of diurnal sleep may develop in an unduly inhibitable brain a situation where inhibition is increased due to conditioning, as in the case of a driver who is conditioned to inhibit his usual run-away-reflex when he hears the sound of a car horn from behind; a narcoleptic driver will fall asleep in such situation; on such examples Levin tries to explain the apparent increase in the incidence of narcolepsy in our machine age with its increased conditioning. Cataplexy is identified with localized inhibition (localized sleep) of cortical motor areas, occurring when either strong aggressive motor impulses are powerfully suppressed because of guilt feelings (e.g.: the man who is about to whip his child), or when an effort is made to ward off an impending sleep attack—in this case the inhibition would be "crowded" away from the substrate of consciousness into the motor areas of the brain. Also a narcoleptic soldier who has to inhibit his reflex of running away is then likely to have a spell of sleep or paralysis, and anybody may then experience a morbid somnolence, fatigue and sleep hallucinosis.

Fabing[15] cites Pavlov's experiments with dogs in the use of an extremely intensive, "ultramaximal" conditioned stimulus, when inhibition occurred instead of stimulation. Through analogy, cataplexy may be understood as a result of a sudden massive ultramaximal stimulus (e.g. anger) which is beyond the maximal limit for the narcoleptic and thus transforms the expected motor excitation into a sudden motor inhibition. This would explain the importance of the element of surprise in the cataplexy. It was also found in dogs that a prolonged repetition of a mild exciting stimulus will eventually cause inhibition (as if through summation into one ultramaximal stimulus): this would correspond to the hypnotic effect of the monotonous sound of rain. Unfortunately, this theory does not explain what makes a narcoleptic brain unduly inhibitable, nor is there anything definite known as to the nature of the inhibition in the central nervous system.

It was only in the 1940's that the psychoanalysts became interested in narcolepsy and a purely psychogenic etiological approach was formed. Prior to that Wilson[46] had suspected that the syndrome of atonia and inhibition could be caused by a variety of factors at different vertical levels of the human psychosomatic structure. Davison and Demuth[11] recalled Freud's idea about the sleep being a re-enacting of the life in utero and stressed its psychobiological protective function against physical and mental exhaustion and for an instinctual equilibrium: a nightly regression, with a temporary denial of reality. This being so it becomes understandable that sleep or its disturbances in some people play the role of a defense mechanism against collision between the instincts and the external world. Thus somnolence may express a retreat—a desire to avoid the unpleasant features of the reality. This idea came to be the cornerstone of subsequent psychosomatic and psychoanalytic investigations of narcolepsy, even though it is frankly admitted that we do not comprehend the chemico-physiological channels through which such a defense reaction could take place, and psychological studies are the only instruments available for this research.

In a classical paper by Langworthy and Betz[21] we read: "The appearance of the (narcoleptic) symptom provided a new fo-

cus of attention and permitted an evasion of a show-down along realistic lines which could not have been avoided if the life themes continued to develop without interruption along the lines already laid down. Central theme in each of these cases is the individual's driving need radically to differentiate himself . . . from the pattern of life which has been laid down for him by others and which he is expected to follow." The ties with the objectionable past are too strong—be it obligation, dependence or seeming unreasonability of a rebellion (which is thus prevented by sleep or paralysis). The narcoleptic illness becomes an alibi —a neurotic defense—where one cannot adjust, cannot compromise, is repeatedly defeated but cannot admit defeat.

Barker[3] finds in his cases through free association at the start of the narcoleptic spells an aggression concealed in laughter, or an angry wish towards a nagging wife. Two of his patients had a deep-seated unresolved hostility towards their fathers and would fall asleep during a sodium amytal interview each time they would be questioned about this painful topic; if one would try to arouse them, they would "stare aggressively at the examiner with all the appearance of a psychomotor seizure."

At this point of understanding Barker finds Kleitmann's theory useful that our wakefulness exists on two levels: 1) the wakefulness of necessity (with a subcortical center in the hypothalamus) which satisfies only internal needs and tensions; and 2) the wakefulness of choice, in which in addition the integrative, goal-determined activity of the cortex is displayed. Sleep ensues when either 1) the subcortical activity is decreased, or 2) the cortical activity is abandoned while the internal tension is insufficient to enforce the wakefulness of necessity. Barker finds that the life histories of the narcoleptics present a wakefulness of necessity rather than the wakefulness of choice, and that their chief need is to deny their dependent strivings. This view is seconded by Goodley[9] who finds psychomotor waves in the EEG of his narcoleptic patient, but without any help achieved with dilantin although psychotherapy brought an improvement and clarified the psychodynamics: a phantasy of a homosexual threat with passive identification with the attacker (which was in a true conversion fashion manifested by the cataplexy). Narcolepsy in that case meant a regression—a symbolic return to the childhood incestual activity with patient's sister. Davison[12] found in his patients through hypnosis a wish to kill or a wish for rape or sexual intimacies in a heavily guilt-laden setting. He explains the pavor nocturnus of children in a similar fashion with added fear of punishment by death. So also are the sleep walkers acting out their unconscious phantasies, for instance, walking towards their parents' bedroom, but the moment the compulsive act is interrupted anxiety reappears. Moonlight in this setting symbolizes the light in the hand of a beloved parent. Davison concludes that such repressed unacceptable wishes create chronical emotional tension which in turn causes a dysfunction of the hypothalamus with resulting vegetative nervous system symptoms including sleep disturbances.

Drake[13] describes a patient who "evades striking back at men by going to sleep"; Roth[38] finds a narcoleptic shackled by a strong attachment to the mother from which the patient is unable to escape into marriage; Van Der Heide-Weinberg[43] in a description of sleep paralysis emphasize the fact that the times "just prior to sleep or on awakening . . . are the times when sexual urges are active and under lesser conscious control." Jones[20] regards cataplexy as a dissociation and recalls Kretschmer's idea about the voluntary half-conscious reinforcement of a reflex of fainting originally resulting in the face of conflict and disgust.

Levin[10] suggests as the best treatment "the deepest psychotherapy possible," but many of the narcoleptics are getting along satisfactorily on dexedrine. No other drug has proven thus far to be of value in the narcolepsy.[1,2,35,46]

Case Report

R.S., a 32 year old male veteran of World War II, was first seen on April 6, 1953, because of alcoholism and strange spells of paralysis. The spells started in 1944 while the patient was in the Navy on a ship transporting ammunition in the Pacific. Patient sustained a head injury without unconsciousness ten months prior to the onset of spells.

The attacks occur always on falling asleep or on awakening. All of a sudden he feels the emotion of a great surprise and tries in vain to get up to prevent a spell. A feeling of fullness in the head initiates "a wave of electricity spreading through the body" and the patient becomes paralyzed. He is terrified and struggles until he is gradually able to grunt whereupon his wife notices the spell and terminates it by shaking the patient. In some (prolonged) spells he saw vividly his relatives entering the room, speaking and walking out with him, yet he knew that all this was only a dream. He usually is restless in his sleep and sensitive to noise. He reported amnesic episodes, deja vu phenomena, and often while in a crowd he had the feeling of he himself being changed, with somebody else—who was also watching him from a distance. He recalled that occasionally while fishing and trying to pull in a large fish he had caught, he would become weak, "I almost fell out of the boat." Morbid somnolence and fatigue stayed with him all the time.

Physical, neurological and ophthalmological examinations were not contributory; studies of blood and urine were negative, as was the X-ray of the skull. EEG-Metrazol test showed "a spike focus in the left temporal region consistent with 'temporal lobe' seizure phenomena." Psychological tests revealed an IQ of 127, with "a great potential for uncontrolled affective discharge which is most threatening to the patient." He appeared at the same time desirous and resentful of being manipulated by other people, and with homosexual ideas. No signs of organicity or psychosis were found, but his potential for a severe anxiety hysteria was judged to be great. The patient was reserved and inhibited in expressing any feelings.

During five months of intensive psychotherapy the patient recalled the story of his life with his deep attachment to his domineering rigid mother who taught him "never to hurt people." This was difficult to follow at puberty when he attempted several sexual escapades with a great feeling of guilt especially when at 19 he went into the Navy. He felt himself destructive and about to be destroyed. When he was betrayed by his first wife whom he later divorced, it was then that the spells started, at the age of 23.

Gradually the patient was able to realize that at bedtime he is fearful and full of destructive, murderous impulses. After he had not had spells for three months, and all other symptoms had left, he desired to leave and was then discharged on September 18, 1953. An out-patient now, he is making a good adjustment, but on some days, usually when someone makes him very angry, the old spells occur again.

We feel that this is a case of a psychogenically caused sleep paralysis in which, thus far at least temporarily, some improvement was achieved with psychotherapy.

Summary

1. The narcoleptic-cataplectic syndrome was described with an attempt to picture the development of our understanding of the mechanism of this syndrome.

2. With regard to the idiopathic narcolepsies, their pathogenesis was described as viewed from the organic as well as psychogenic standpoint.

3. Case of sleep paralysis was reported.

4. The conclusion seems to be that the psychogenic component cannot be disregarded in the etiology of the idiopathic narcolepsies, even though we do not know today whether it serves only as a trigger mechanism[10] on a pathologically predisposed organic substrate, or whether it is in itself the sole causative agent.

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Contribution of Carbonic Anhydrase to Sensitivity of the Central Nervous System and to Carbon Dioxide Therapy

WINIFRED ASHBY, PH.D.
Washington, D. C.

Two authoritative discussions of carbon dioxide therapy have come from the press recently. One is by Dr. Meduna, who has extensively applied this therapeutic tool,[11] the other by Gellhorn,[7] who has done much toward the elucidation of shock therapy. In neither of these discusisons is mention made of the enzyme carbonic anhydrase of which carbon dioxide is the substrate. It is my purpose to introduce carbonic anhydrase into the picture.

There are two enzyme complexes in the brain that have to do with its activity rather than with its maintenance. One of

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From St. Elizabeth's Hospital, Washington, D.C.

these is the acetyl choline—choline esterase complex, the other carbonic anhydrase-carbon dioxide. Both show significant loss of activity as pH is reduced within physiologic limits at body temperature.[12,5] But while reduction in activity of choline esterase would result in the longer life of acetyl choline, causing greater neuronal activity, reduction of carbonic anhydrase would either decrease activity by reducing the rate of carbon dioxide removal, or reduce the rate of potassium turnover, thus probably decreasing potential.

Acetyl choline and its associated enzymes have been extensively studied with reference to the activity of the nervous system; carbonic anhydrase has not, in spite of the fact that choline esterase is more abundant in the lower centers of the central nervous system and carbonic anhydrase in the higher, which one might assume indicates their relative importance in the process of thinking.

The high metabolic rate of the brain,[8] the increase in proportion of glycolysis upon stimulation,[13] with the reported insufficiency of the increased blood flow to remove the increased heat produced in a stimulated area,[13] would suggest a function for an enzyme capable of catalyzing the hydration of CO_2, since carbon dioxide, according to the studies of Lorente de Nó,[10] has a specific effect upon nerve function. The carbonic anhydrase content closely parallels the oxygen uptake as found in vitro in different areas of the central nervous system.[1] In addition to its occurrence within the neurones, its distribution is such that the presence of the enzyme in accessory cells is indicated. In the primates there has been developed an unusual relationship between the carbonic anhydrase content of the cortex and of the white matter beneath it.[4] The white matter may contain more than the cerebral cortex, an excess of the order of 50%. This is true only in the correlating areas and would seem to be an evolutionary advance. The simplest explanation of this distribution would be that carbonic anhydrase is also stationed outside the neurones. If there are such accessory cells containing carbonic anhydrase in the primate white matter, it is possible that they may be found in the cortex. However, unless the concentration of carbonic anhydrase is lower in the neurones than in red blood cells, quantitative relationships would not give strong support to an argument for such extraneuronal sites. The cortical content in nine comparisons in man averaged 4.5% of the packed red cells and a comparable figure was found for other species, while Gerard estimates that the brain is 3% neurones.

By means of extraneuronal sites of carbonic anhydrase, the readily permeating CO_2 could be anchored by changing it to bicarbonate, thus producing an immediate gradient away from the active neurones. The bicarbonate would be exposed to the removal facilities of a greater capillary network than immediately surrounds the neurone, thus complementing the effect of increasing blood flow. This mechanism, however, may be peculiar to the correlating areas of the primate brain.

Proof that there is carbonic anhydrase functioning within the neurone rests upon some recent work of Krebs and his associates.[6] They have shown that in cortical slices carbon dioxide, by its ability to combine with water to form ions, performs the ferrying action found in the kidneys and other tissues in which ions are transported against a gradient. It was found that potassium, initially lost from brain slices, was restored upon incubating in the presence of l-glutamate, glucose and oxygen. L-glutamate was essential and was taken up in quantities approximately equal to the potassium. Balance of the ionic shifts of sodium, potassium and glutamate required that other ions migrate into the material studied. Since an inhibitor of carbonic anhydrase slowed down the recovery, it was evident that the ions formed in the hydration of carbon dioxide are involved. With labeled potassium a high rate of potassium exchange was found after recovery from the initial loss. This rate was decreased by inhibition of carbonic anhydrase.

Before this work appeared, proving that carbonic anhydrase is within the neurone, I considered that the findings of Lorente de Nó on the effect of CO_2 upon peripheral nerve conduction might explain the function of carbonic anhydrase, which is found in greatest amount in the dominant areas of

the central nervous system. It seemed probable that carbonic anhydrase, by removing CO_2 from the firing neurones maintained a decreased threshold of stimulation and an increased rate of conduction and that the higher centers dominated because of this greater potential activity. Maintenance of low CO_2 seemed to be best accomplished by extraneuronal sites of carbonic anhydrase activity.[3] From this point of view I would explain the lower threshold of hearing, decline of visual function and deterioration in mental operations, reported by Gellhorn with non-narcotic doses of carbon dioxide, as evidence of an amount of gas beyond the complete control of the enzyme, while the excitatory effect, shown by Gellhorn to be due to an upward discharge, I would assign to the effect of the reduction of pH upon choline esterase, which is present in greater amount in lower centers. The effect of 30% CO_2, which produced unconsciousness but did not inhibit conduction over the long tracts, would seem to be capable of explanation by the fact that conduction of an impulse will take place in the presence of even 90% CO_2 and by the assumption that, at 30% carbon dioxide concentration, the gradations of activity of carbonic anhydrase, determining the relative responsiveness necessary for consciousness, are obscured.

The work of Krebs, however, has moved carbonic anhydrase into the neurone and has associated it with the maintenance of potassium content. On this basis it would seem possible, if potassium plays a role in maintaining the resting potential, that the greater the amount of carbonic anhydrase present in the neurone and the greater the metabolic rate—the two show a parallelism—the greater will be the rate at which potassium enters, and since there is a continuous turnover, the greater will be the resistance to firing and the higher the spike potential. In this event, the dominant areas, which have the greater amount of carbonic anhydrase and the greater metabolic carbon dioxide production, would not respond to those with a smaller content and a lower spike potential, but by means of their own greater spike potential, would be able to fire the neurones of lower carbonic anhydrase content, which because of their lower rate of potassium turnover, maintained a lower threshold of stimulation. For an upward discharge the lower neurones would have to reinforce one another.

The advantage of what is probably an extraneuronal site of carbonic anhydrase found beneath the primate cortex in correlating areas might be that, due to maintenance of low carbon dioxide there would be a reduction in the spike potentials of axones from neurones of the cortex as they passed through to re-enter the cortex and in consequence it would take a larger number of active neurones to fire an individual, thus assuring a higher degree of correlation. The motor area does not have this increased amount of carbonic anhydrase beneath it.

To explain the loss of consciousness produced by 30% carbon dioxide, one might assume that, in the neurones with the greatest carbonic anhydrase content, the threshold of stimulation has been built up to such an extent that they cease to fire, or there is the possibility that the considerable effect of decreased pH upon carbonic anhydrase activity may have destroyed the dominance of the neurones with the greater carbonic anhydrase content. The assumption that neurones containing more carbonic anhydrase have a higher threshold of stimulation and greater capacity to stimulate other cells, would explain the effect of 30% carbon dioxide upon the dementia praecox patient in the catatonic state, first demonstrated by Loevenhart, Lorenz and Waters. The brain of the praecox patient has a low carbonic anhydrase content. We will assume that it is insufficient to develop spike potentials large enough to fire the lower centers, therefore he remains immobile. His period of normality comes after he has been breathing deeply and has had a chance to blow off excess somatic CO_2, but in the meantime, carbon dioxide, which readily passes the cell membrane has entered the neurones and is compensating for the low carbonic anhydrase to increase potassium uptake to a point at which the upper levels can stimulate the lower, and for a short time the patient functions normally.

Meduna reports success in treating psychoneurotic conditions with repeated doses of 30% carbon dioxide in oxygen. He has

not found the treatment effective in cases of psychosis.

Dr. Meduna considers that reverberating systems are set up which can not discharge normally and that any decrease of threshold of stimulation of the feedback mechanism prevents successful homeostasis. He considers that carbon dioxide is successful because it raises the threshold of stimulation of the feedback mechanism, but he does not explain how any permanent result can follow the treatment, which lasts only a few minutes.

I suggest that the permanent effect may be obtained by change in the content of carbonic anhydrase, of which carbon dioxide is the substrate. Bacteriologists expect an enzyme to increase in bacteria grown on its substrate. I, therefore, tried to increase carbonic anhydrase in rat brains, using carbon dioxide, but I must confess that the result appeared to be a decrease. The experiment needs repeating. Killum and Schaefer, using 30% carbon dioxide on guinea pigs, recently reported a decrease in blood and an increase in kidney.[9] They state nothing concerning the brain. Since the body tends to heal itself, a change in carbonic anhydrase content might either increase resistance of the feedback mechanism or decrease resistance of the output.

Toward an explanation of the failure of carbon dioxide to be effective in the treatment of psychoses, let us say dementia praecox and other conditions with a depressed activity, may I offer the following: According to my experience the carbonic anhydrase content of the brain in this group is likely to be low.[2] It is probable that it is low, because the capacity to form it is not normal and this reduced capacity is due to a deficiency. It is also probable that the necessities of the hemopoetic system will give us a clue to this deficiency. If the effect of carbon dioxide is to stimulate the production of carbonic anhydrase, it still would not supply the deficiency. If its effect is to reduce carbonic anhydrase, it would be harmful.

I have attempted to re-evaluate the part played by carbonic anhydrase in the functioning of the brain in terms of the recent work of Krebs, but any reliable explanation must await knowledge as to the chemistry of the passage of a spike potential. This recent work, however, in conjunction with the peculiar quantitative distribution, which I have previously described, and the decreased content in certain abnormal mental conditions, should make it evident that carbonic anhydrase rates a greater share of the attention of neurophysiologists than it has received to date.

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On the Natural History of Hysteria in Women

(A Follow-up Study Twenty Years After Hospitalization)

DEWEY K. ZIEGLER, M.D., and NORMAN PAUL, M.D.
Boston, Massachusetts

The proper classification of psychiatric disease is, and has been for some time, a hotly debated subject. The many assays at the task are in reality attempts to define or give meaning to psychiatric terminology and they indicate the major linguistic difficulties with which modern psychiatry is struggling. The obvious effect of this semantic confusion is to interfere with the solution of the two major problems; etiology of symptoms, and evaluation of therapy. For example, before the results of a certain type of treatment in "paranoid schizophrenia" can be checked it must first be ascertained that this term is sufficiently precise to guarantee that different observers using the same term as a symbol will select a similar group of patients.

Medical terms gain precision in meaning in proportion to the amount of data to which they refer. The names of the infectious diseases have fairly precise meaning because much is known of their etiology, pathology and physiology, and much can be accurately predicted as to their course with and without treatment. In all these respects the names of psychiatric disease entities refer only to a comparatively small and fragmentary collection of data that is well known and agreed upon. Beyond this there is controversy or complete darkness.

The present investigation was designed to obtain a generous sample of the life histories of a group of women who were given the diagnosis "psychoneurosis hysteria" at the Boston Psychopathic Hospital, in the years 1927-32. It is hoped that this data will contribute to the meaning of the term psychoneurosis hysteria as it was used in those years—"meaning," that is, in terms of what are the predictable possibilities for a group of patients so diagnosed.

The diagnosis "hysteria" was selected for several reasons:

a) The course of patients with psychotic diagnosis has already received much more attention than that of patients with neuroses, at least as with respect to hospital admissions.
b) Heated disagreements exist as to the results of therapy in neurotic patients in particular, and
c) The term "hysteria" is distinguished by a singularly chaotic semantic history and by having been singled out as identifying a patient group particularly suitable for psychoanalysis.

Material and Method

The records of all female patients, who were given a final diagnosis of psychoneurosis hysteria when discharged from the Boston Psychopathic Hospital in the years 1927-32 were used. Over this 5-year period there were 66 such patients. These were all in-patients and their period of study varied from that of a few days in one or two cases to several months in others. All of them were seen by one or more staff psychiatrists. Every effort was made to discover the course of these patients' lives subsequent to their discharge from the hospital, with regard to their physical and mental health. Records of hospitalizations in mental and in general hospitals were obtained, the ex-patients themselves were interviewed in their homes when they could be found and were willing to be interviewed. In the case of patients who had died, relatives, friends, and business associates were interviewed.

Patients were questioned concerning recurrence of conversion symptoms, occurrence of phobias, compulsions and obsessions, anxiety symptoms, any type of illness, operation or previous hospitalization. Questions were asked to determine something about the patient's life routine, domestic and social adjustment. The interviewers then attempted a cursory evaluation of the ex-patient's domestic and mental status.

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From the Boston Psychopathic Hospital and the Department of Psychiatry, Harvard Medical School, Boston, Massachusetts.

Results

1. Nature of Follow-up Data:

The major sources of follow-up data are indicated in Table I.

TABLE I

NATURE OF FOLLOW-UP DATA

Source		*Cases*
Patients interviewed		35
a) Interview satisfactory	28	
b) Interview brief	5	
c) Patients psychotic	2	
Patients dead—Relative interviewed		15
Patients Living — Relative or friend interviewed		6
Scattered information — 1-10 years after observation		6
Patients lost		4
Total		66

In the 5 cases labelled "brief interview" the authors felt that the ex-patients were concealing information.

Information obtained from relatives concerning patients who had died tended to be full and frank, that concerning living patients tended to be fragmentary and probably unreliable. "Scattered information 1-10 years after observation" refers to hospital records consulted, and comments from relatives or friends.

2. Cause of Death:

The cause of death was ascertained both from interviews with relatives and from hospital records in all except 3 cases, and are listed in Table II.

TABLE II

CAUSE OF DEATH

(*Indicates death within 5 years of original hospitalization.)

		Cases
Carcinoma		3
Breast	1*	
Stomach (in old ulcer)	1	
Uterine	1	
Unknown Cause		3 (1*)
Progressive Neurological Disease (? Multiple Sclerosis)		2*
Coronary Thrombosis		2
Rheumatic Heart Disease with Failure		1
Hepatic Cirrhosis		1*
Pulmonary Tuberculosis		1*
Addison's Disease		1
Suicide		1*
Total		15

Of those dying within 5 years following hospitalization, 4 showed symptoms of the fatal illness during hospitalization.

3. Subsequent Psychiatric Disease:

TABLE III

SUBSEQUENT PSYCHIATRIC HISTORY

	Cases
Re-hospitalized later with Diagnosis of Psychosis	22
a) Severe, protracted psychoses	7
b) Acute, self-limited psychoses	11
c) Psychoses with psychopathic personality	4
Rapid disappearance of original symptoms, no recurrence	12
Minor complaints of "Worry," "Nervousness," etc.	10
Recurrence of frank somatic conversion phenomena	4
Insufficient data	18
Total	66

The histories of those patients who showed a favorable course will be discussed in detail in a later communication. Here we wish to examine more fully problems connected with the group of 22 patients (⅓ of the original group) who were readmitted at least once to another mental hospital with a diagnosis of psychosis.

The specific psychiatric diagnoses are seen in Table IV. Of this group of 22 patients, 13 were interviewed in person, 5 had died and complete records up to the time of death were obtained, and in the remaining 7 partial data (including state hospital records) were obtained.

TABLE IV

DIAGNOSES ON PATIENTS SUBSEQUENTLY RE-HOSPITALIZED WITH DIAGNOSIS OF PSYCHOSIS—1928-52

	Cases
Dementia Praecox	12
Paranoid	6
Catatonic	1
Simple	1
Hebephrenic	1
Other types	3
Manic-Depressive Psychosis	9
Depressed	5
Manic	4
Organic Psychosis	2
Psychosis with Psychopathic Personality	1
Total	24

(NOTE: The discrepancy between the total 24 here and 22 in Table III is due to the fact that one patient was diagnosed schizophrenic on one occasion, manic on another, depressed on a third.)

A large number of patients had several hospital admissions; there were 33 total sub-

sequent hospital admissions with the final diagnosis psychoneurosis hyteria, 18 admissions with the diagnois dementia praecox and 12 with manic-depressive psychosis.

The age of initial hospitalization of these 22 patients, who were subsequently re-hospitalized with a diagnosis of psychosis is seen in Table V.

TABLE V

PATIENTS ORIGINALLY DIAGNOSED HYSTERIA SUBSEQUENTLY PSYCHOTIC

Age on original admission	*Number of patients*	
10-20	12	(54%)
21-30	5	
Over 31	5	(23%)
Total	22	

For comparison Table VI shows the age of initial hospitalization of a larger group of patients, all living, in whom good follow-up data ascertained that no subsequent psychotic illness or hospitalization for mental disease had taken place.

TABLE VI

PATIENTS ORIGINALLY DIAGNOSED HYSTERIA NOT SUBSEQUENTLY PSYCHOTIC

Age on original admission	*Number of patients*	
10-20	8	(24%)
21-30	10	
31 and over	16	(48%)
Total	34	

The significance of the age of onset of illness is pointed up by the fact that on 27 patients who were under 25 when first hospitalized and alive at the time of the follow-up study (3 had died), 13 or 48% had had subsequent sojourns in mental hospitals, all except one with a diagnosis of psychosis.

4. Nature of Subsequent Illness:

Far more important than the diagnosis, of course, is the specific amount and type of disability suffered by the patient. Although the greatest disparity in life histories was present, three general types of psychiatric illness may be described.

a) Chronic, protracted, disabling abnormality—severe psychosis. Seven patients fell into this group. Two of them never left mental hospitals, became progressively more out of contact with surroundings following their original period of observation at Boston Psychopathic Hospital; both are now dilapidated, muttering, posturing, back ward patients. Both were seen personally. It is interesting, parenthetically, that there is a strong suspicion of gross organic brain disease in both of these patients—one has frequent grand mal convulsions, the illness in the other began with torticollis following a febrile illness in 1918 (? influenza).

A third patient (now dead of rheumatic heart disease) was in and out of mental hospitals, during most of her forty years. Her behavior was bizarre, ranging from the querulous and demanding to the obstinate, accusatory and assaultive, and she was diagnosed as "Dementia Praecox paranoid." This patient also may well have had brain pathology. Her illness began at age 9 with "rheumatic fever and diphtheria" followed by chorea and by right-sided convulsions which persisted from that time to her death at forty of rheumatic heart disease.

Two patients in this group, after protracted hospitalization—one for a stuporous psychosis called depression, the other for an agitated schizo-affective disorder — were given pre-frontal lobotomies, with subsequent ability to leave the hospital, and maintain some kind of employment for the subsequent 3-4 years. Both were interviewed in their homes; one was moderately jovial and hyperactive, the other showed normal behavior although living in the most wretched circumstances.

The remaining two patients, who spent years in mental hospitals with the diagnosis of psychosis, are interesting in that they demonstrate the unpredictable recoverability of the psyche, even after prolonged illness.

C.D.—For 15 years was hospitalized with a paranoid psychosis—she felt that God's voice came through her mouth without control, and that other voices were speaking to her to which she constantly replied. She bitterly resented her whole family, blaming them for her illness and hospitalization. Gradually she lost the hallucinations and after the death of her husband, no longer had outbursts of agitation. At age 63 she was discharged from the hospital and is now holding increasingly responsible positions as a practical nurse, leading an active social life, and is asymptomatic—a cheerful, alert woman.

F.B.—Always an irritable and bizarre spinster, gradually became more extreme in her behavior, wandering aimlessly from one job to another ac-

cusing all employees of trying to rape her, living on bananas and milk. When eventually hospitalized her gait and manner were extremely "odd" and she used chiefly legalistic vocabulary in conversation. After more than a year of hospitalization she was discharged, obtained a good job "to prove she could do it," married her old guardian, and many years later wrote a friend a cheerful, normal letter of news, with no complaints.

b) Acute self-limited psychoses, often recurrent, usually involving mood disturbances, and quickly terminated by electric-shock treatment, was a second type of illness encountered. Of 11 patients who could be thus classified, 5 were seen personally. All 5 were placid and cooperative in the interview situation, and lived comfortably with their families. In none, between "attacks," were there complaints that could be called "neurotic."

c) A few cases developed psychotic episodes in the course of a turbulent life history of rebellion and anti-social behavior that is generally labelled "psychopathic personality." These are individuals about whom doubt always exists as to whether to call the diagnosis hysteria, malingering, "psychosis with psychopathic personality" or Ganzer's Syndrome.

Discussion

1. Accuracy of Original Diagnosis:

To return to our original problem—what does data on this group of patients contribute to our knowledge of the meaning of the term "hysteria"? The question immediately arises, "Were all these patients *truly* hysterical when first seen twenty years ago or was a mis-diagnosis made at that time, and is this follow-up study therefore unrelated to hysteria? To answer this question we must compare findings of this group, when originally seen, with the currently accepted definition of hysteria.

The definition of hysteria in recent editions of the American Medical Dictionary and the American Psychiatric Dictionary may be subsumed under four different headings.

A. "A diagnostic term referring to numerous symptoms which may involve any physical apparatus of the body . . ." or "psychiatric symptoms of any type . . . amnesia, fugue, somnambulism, delirium, anxiety, etc."

B. "A psychogenic disorder . . . less incapacitating than a psychosis, resulting only in partial disorganization of the psyche."

C. "A consequence of a conflict in the unconscious division of the psyche . . . the classical subject matter for psychoanalysis."

D. "Lack of control over acts and emotions . . . exaggeration of the effect of sensory impressions . . . simulation of various disorders."

A. *"Numerous symptoms which may involve any physical apparatus of the body."* —Fourteen of these 22 women had such clearly defined somatic symptoms, the most common one (8 cases) being episodic fainting spells, or clonic movements of the whole body, or half the body. Two patients had abdominal pain, and one each suffered from anesthesia of a limb, twitching and hyperesthesia of one hand, "hot flashes" (possibly related to menopause), muscle rigidity. The remainder had only psychological manifestations (two had amnesia) of varying types.

B. *"A psychogenic disorder less disabling than a psychosis:"*—All of these cases were considered to be "psychogenic" by the examining doctors, i.e., emotional maladjustments were discovered and described in all, and in none was there considered to be brain or other bodily disease. The disorder was considered "less disabling than a psychosis" at the time—1927-32. Three were transferred to other hospitals, the others went home. Clearcut delusions or hallucinations were present in only 3 on admission. Mood disturbances of varying severity were present in several others, but all of these psychiatric symptoms are admitted into the concept hysteria.

C. *"A consequence of conflict in the unconscious . . ."*—From the point of view of 1927-32, in only a few cases was this criterion explicitly stated as having been used in the diagnosis. In looking at the clinical records in retrospect, one cannot use it. It is striking however, that in several cases with rather severe psychiatric manifestations (hallucinations, delusions), it appears as if the diagnosis hysteria was made only because the emotional meaning of the symptoms seemed clear. There was a marked tendency to call an illness "neurotic" rather than psychotic in proportion to the degree to which doctors became interested in the psychodynamics of the case.

D. *"Lack of control, exaggeration . . ."*— In all but a few cases it was this criterion which was paramount in making the diagnosis. Almost all patients were constantly described as "childish," "naive," trying to attract attention," "self-dramatizing."

In summary then, this group, when originally seen in the years 1927-32, satisfied the accepted diagnostic criteria of hysteria.

By virtue of selecting only hospitalized cases for this study we may of course have been dealing with a more severely ill group of cases than would be encountered on an out-patient basis. The diagnostic problem, however, is the same—and even with this group comparative mental health has been the outcome in about one-half of the cases.

2. The Problem of the Definition:

The fact that these cases were thought to have a kind of uniformity 25 years ago but now show the most extreme diversity in mental status raises the question of whether the given criteria for the diagnosis are not so imprecise as to be non-functional; whether they do not create the illusion of defining an entity where there is none.

It is unfortunate that the definition of hysteria is static, and does not involve the concept of time or course of illness. The data disclosed by this study indicates that, if the life-course is considered, the line between hysteria and psychosis is, in this large group of cases, indistinguishable, and the process of dividing mental disease into "disorders"— the more disabling being called psychosis, the less disabling being called "neurosis"—is futile. All of these 20 patients were subsequently enough disabled to be called psychotic. The inadequacy of the definition is underlined by the study of Hunt, Wittson and Hunt,[5] who found that between 2 groups of psychiatrists attempting to place patients in three major categories (psychosis, psychoneurosis, and personality disorder) there was agreement in only 54.1% of cases.

There are equal but different difficulties if one relies on the presence of "conversion symptoms" to make the diagnosis. It is unfortunately more than difficult to diagnose correctly somatic disease as neither organically determined nor conscious malingering. Life histories revealed that organic disease was frequently missed. In 5 patients with seizures, for example, subsequent developments made more or less certain the diagnosis of epilepsy. (2 patients had increasingly frequent generalized seizures, with "schizophrenic" deterioration in one case, and rapidly developing signs of diffuse central nervous system disease and death in the other case.) One patient with frequent right-sided clonic movements and speech difficulty subsequently developed complete right spastic hemiparesis with aphasia. One had persistent right-sided seizures following chorea in childhood, and a third had a strong family history of seizures.) It is fair to presume that this is only a fraction of organic disease which may have been present.

We know that the encephalitis of the early decades of this century left in its wake severe behavior disturbances.[7,4] It has also recently been claimed that rheumatic fever can affect the brain by causing a chronic rheumatic encephalitis[1] and chronic vascular disease related to subsequent psychoses.[3] In this connection the past medical histories of the 22 patients who were subsequently psychotic were compared with those of a parallel group in this series who were not subsequently psychotic (personally interviewed). The results are seen in Table VII and show a striking discrepancy between the two groups. This does not prove, but strongly suggests that unsuspected organic brain disease was a factor in the more serious illness of the one group.

Concerning malingering, it is impossible to know its incidence by subsequent data. Two patients with amnesia, however, and one with anesthesia of a limb, had subsequent history of "psychopathic personality."

TABLE VII

PAST HISTORY OF INFECTIOUS DISEASE

	In 22 patients subsequently psychotic	In 22 patients not subsequently psychotic
Definite rheumatic fever or chorea in childhood	3	1 (St. Vitus dance)
Definite influenza 1918-1920	4	0
Probable influenza by history	2	0

The definition of hysteria in terms of a conflict in the unconscious with resultant repression of instinctual drives and the symbolic use of the body also has flaws. Again this is the description of a patient at a fixed moment and is not dynamic. Inasmuch also as evidence of the life of the unconscious is elicited only after much time and effort and the data obtained is a matter for interpretation and dispute, accurate diagnosis of hysteria using this criteria would seem to be tedious if not well nigh impossible. Whether it is the "classical subject matter for psychoanalysis," as the American Psychiatric Dictionary says, is difficult to say, when there is doubt as to the meaning of "it".

Lastly as a practical matter, it was found that psychiatrists usually tended to equate the term hysterical with the adjectives histrionic, attention-getting, self-indulgent—all involving the implication that the patient could control the symptom at will. This distinction, however, between those patients who are, and those who are not, dramatic is not useful, and has been recognized as a frail reed on which to lean in psychiatric diagnosis ever since Bleuler called attention to the identical phenomenon of "pseudo-malingering" in association with the more malignant disease he called schizophrenia.[2]

Such, in summary, are the uncertainties and ambiguities in the current use of the term hysteria. Such difficulties are important in that they interfere with communication of information.

As a remedy for this semantic confusion, some investigators[6] have recommended that the use of "hysteria" be restricted to what is felt to be a well-defined clinical entity characterized by repeated illnesses of certain kinds in women of infantile build and dependent personality. It does not seem probable, however, that the use of the word can be so restricted. Would it not then be more profitable to describe patients in terms of multiple concrete discrete items in their physical and mental status—leaving such psychiatric categories as hysteria, with their poorly understood etiologic and prognostic implications, to a time when we know more of etiology and prognosis.

Summary and Conclusions

1. Of 66 hospitalized female patients diagnosed "psychoneurosis, hysteria," 20-25 years ago, 22 were found to have had a subsequent illness diagnosed as psychosis.

2. All types of psychosis occurred, paranoid schizophrenia predominating.

3. Youth on hospitalization for the original (hysterical) illness was positively correlated with a higher rate of hospital readmission.

4. The records of 22 cases, in retrospect, filled most of the present-day criteria of definition of "psychoneurosis hysteria."

5. Central nervous system disease, particularly epilepsy, was frequently mistaken for hysteria. Incidence of childhood encephalitis and rheumatic fever was much commoner in the group subsequently psychotic than in a "control group."

6. Of the diagnostic criteria for hysteria originally used, the one most relied upon was that of exaggeration of symptoms and self-dramatization.

7. The ambiguities in our usage of the term "hysteria" and the need for more concrete description of patients is emphasized.

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Treatment of Cerebral Fat Embolism

DEWITT W. BROWN, M.D.
Indianapolis, Indiana

I shall present a short summary of the clinical entity of cerebral fatty emboli, two typical cases of widely varying severity, and a treatment program that has seemed to be successful in five of six cases seen in Indianapolis in the past 22 months.

Embolism of fat globules to the brain should be strongly suspected in cases of injury to fatty tissue or bone marrow that show rapidly developing signs of cerebral pathology within the first few days of injury. It is most commonly believed that bone marrow fat is forced into damaged veins through which it is transmitted to the lungs where symptoms similar to bronchopneumonia may be produced. Some of the fat seems to pass through the lungs into the systemic circulation and to lodge in the brain and other tissues of the body. In typical cases free fat droplets are found in the sputum and may appear in the urine within two to six days. Some clinicians claim to have observed fat in the eyegrounds in the circulating blood, as well as in hemorrhages and exudates. Examination of the venous blood may show large fat droplets. Petechial hemorrhages of the anterior thorax, abdomen and to a lesser extent on the extremities are characteristic of the complication. The diagnostic criteria most commonly used are: history of injury to bone marrow or fatty tissue, rapid onset of cerebral symptoms, petechial hemorrhages, and free fat droplets in the sputum and in the urine.

The literature concerning cerebral fat emboli is extensive and Schneider's publication[1] is particularly excellent. Most of the articles published are case presentations. Apparently only one voice has been raised against the clinical entity; Whitson,[2] in a "Critique of Fat Embolism," feels that there has been no convincing proof in favor of the theory of fat embolism, and feels the diagnosis should be eliminated in favor of "anoxemia." His arguments are quite well presented, and if nothing else the disorder is something that has been almost universally accepted as existing but which has been studied incompletely. This exists despite a situation in which fatty emboli are held responsible for a large proportion of fracture deaths.

That the diagnosis can not be made on the finding of fat in the urine alone has been demonstrated by several orthopedists who have found fat droplets in the urine of 70-80% of their trauma cases. Another fly in the diagnostic ointment was a recent study[3] of 60 speciments of bronchial sputum and 25 of oral sputum in presumably normal individuals. All of these had fat globules and it was concluded that fat is a normal constituent of sputum.

A study from the Armed Forces Institute of Pathology[4] offers strong evidence that the pathological entity does exist. They demonstrated 27 cases of bone marrow embolism to the lungs. Of 203 consecutive autopsy cases with multiple fractures 6% had bone marrow embolism. Of interest is that 7 of these resulted from convulsions and 3 of the cases from vertebral fractures from shock therapy.

Even if the pathology is in doubt, the clinical picture does exist and has been felt to be fatal in up to 80-90% of the cases.

The first case is that of a 20 year old female who was struck by a car one evening at 5 p.m., suffering a comminuted fracture of the left tibia and a ½ inch scalp laceration in the right parietal area. On admission to the hospital she was alert, and there was no history of unconsciousness. Fracture was reduced under pentothal 2 hours after injury. She was awake the next morning and talking to the nurse. Thirteen hours after injury she expressed sudden apprehension to the nurse and lapsed into coma. Her pulse became rapid to 130 and respirations rapid and shallow. Four hours later she had a grand mal convulsion. When I examined her 21 hours after injury, she was comatose but able to open her eyes on sharp command. The eyes did not track together;

her pupils were widely dilated but reacted to light; there was bilateral mild papilledema. Her face was symmetrical and the jaws were clenched. Breathing was difficult and she vomited partially changed blood. There was no nuchal rigidity. Her arms were kept in flexion and the fingers flexed. There was ankle clonus and a positive Babinski on the right. The left lower extremity was enclosed in a cast. She also had a bilaterally positive Hoffmann.

At that time we did not have the night nurse's report of rapid coma following a lucid post-anesthesia period and we erroneously believed she had gradually become more comatose since the injury. In that false light her case was fairly typical of epidural bleeding. Skull films showed no evidence of fracture. Twenty-four hours after the injury, four burr holes were done by Dr. John Hetherington but no epidural or subdural hematoma was found. It was his opinion that the brain appeared very wet. The following day her condition was much the same and the case was considered critical with a poor prognosis. Lumbar puncture the day after craniotomy revealed a pressure of 180 to 240 mm. H_2O with rapid and frequent fluctuations. The blood-tinged appearance of the fluid was ascribed to her surgery. The fluid contained a faint trace of globulin, protein 34, sugar 108 mgs.% and 4500 red cells with 2 white cells. Blood sugar on the day after the injury was 142 mgs.%. N.P.N.s on the first three hospital days were 53,47 and 32. Two days after injury her urine was negative for fat but three days after injury fat globules were found in her urine. Chest X-ray two days after injury showed, "Small areas of decreased areation on both sides. This is felt to represent bronchial pneumonia."

Oxygen by nasal catheter and later by oxygenaire was used from the first day of cerebral symptoms. Feedings were done through an anchored levine tube and an aspirating machine was kept at the bedside. Special nurses were in continual attendance. Patient's condition remained unchanged and critical for 8 days.

In view of Karsner's theory[5] that the resolution of fatty emboli is brought about by the calcium ions of the blood, on the 7th day the patient began to receive daily injections of 10% calcium gluconate. It is not known whether that drug was of help, but the following day her mental condition began to improve remarkably, and she was able to make her first pertinent verbal response within a few minutes after the second injection.

Petechial rash appeared on the 8th day. Jaundice began to develop on the 8th day after injury and the following day her icteric index was 36. Since the blood count on admission had been normal with a hemoglobin of 90% and there had been virtually no blood lost at the time of injury, the count was not repeated until the 9th day, at which time we were surprised to find a hemoglobin of 43% with a count of 2,300,000. As soon as transfusions were started she began her second leap in improvement, and recovery was so rapid that she was able to be released on the 20th day. At that time no neurological sequela were present except the dilatation of the pupils and diminished visual acuity which could be corrected by pupillary constriction. Her father felt that her mental condition was better than before the injury. The pupillary dilatation subsided a few months later. Treatment of this case consisted of: Oxygen, levine feedings, constant nursing care, penicillin, parenteral vitamins, intravenous calcium gluconate, nicotinic acid and blood transfusions.

The second case is that of a 29 year old male who was admitted one evening at 8 p.m., having suffered a comminuted fracture of his right tibia and fibula shortly before. Fractures were manipulated under pentothal the same night. There was no history of head injury associated with the leg fracture. Patient was alert until about 30 hours after admission when he became increasingly lethargic and 38 hours after admission was confused and disoriented. A petechial rash appeared on the anterior thorax and abdomen about 40 hours after admission.

Neurological examination at that time was of a lethargic, completely disoriented male. There was a wide spread petechial rash, the lesions of which measured ½ to 2 mm. in diameter on his chest, abdomen, anterior thighs and several larger spots in the palpebral conjunctiva. Neurological abnormal-

ities were as follows: Right biceps slightly more active than the left, absent abdominal reflexes, positive Babinski and Oppenheim on the left. The right lower extremity was encased in a plaster cast. Fleeting glimpses of the retinal vessels suggested occlusion of some of the arteries. Respiratory rate was about 30 with some coarse rales in the left chest. Lumbar puncture at that time showed an opening pressure of 272 mm. H_2O. Spinal fluid had a protein of 14 with 1 cell. Sugar was 85, Mazzini negative, smear for organisms negative and fat globules were demonstrated in the spinal fluid. Urine was negative for fat on the day that his stupor began, but fat was found in the urine on the following day and daily until the day before his release 16 days after admission. Three days after admission he seemed more alert but was still poorly oriented and his neurological signs were the same. Four days after admission he was completely oriented but still showed some lethargy, clouding of consciousness and euphoria. The Babinski and Oppenheim were negative. It was felt that the prognosis was fairly good. Six days after admission the rash had become brown instead of red; he was clearer mentally but incapable of abstractions. Sixteen days after admission he was mentally clear and able to do serial seven's quite well.

X-ray of this patient's chest was negative. Because of the experience of hemoglobin loss in the preceding case, his blood levels were watched closely. On the day of admission, his hemoglobin was 87%, three days later 80%, four days later 73% and six days after admission was down to 61%.

Treatment of this case consisted of two or three injections daily of 10% calcium gluconate beginning the first day of neurological difficulty, parenteral vitamins, and intravenous fluids. Blood transfusion and nicotinic acid were also used but these were started after his improvement was well under way.

The literature is virtually devoid of any concise treatment program for cerebral fatty emboli, and the emphasis is on treatment at the fracture site by such things as tourniquets, venous ligation, evacuation of the fatty pool at the site of injury and immobilization. Other more specific things that have been attempted have been intravenous sodium carbonate, which was felt to be too dangerous, sodium desoxycolate, the results of which were inconclusive, ether inhalation, and nicotinic acid as a vasodilator. Stellate ganglion block was used on one case with transitory but definite improvement.[6]

In addition to these two cases, Dr. Hetherington invited me to observe four other cases of cerebral fat embolism in the past 18 months. In most of these cases we were struck with the marked need for oxygen that these patients have and the frequency of hidden blood loss. Nothing was found much more important than to alert the attending private duty nurse to the need of frequent and efficient aspiration of the throat. Intravenous calcium gluconate was used empirically in all of these cases.

It is felt that a treatment program in general would be that of cerebral edema and anoxia with particular emphasis on the oxygen and blood needs and an attitude that if these patients can be kept alive for perhaps a week the prognosis is good. Such a treatment program would include: Oxygen, daily attention to the need for transfusion, frequent aspirations, constant nursing care, intravenous calcium gluconate, anchored levine or tracheotomy in the unconscious patient, prophylactic antibiotics, parenteral vitamins and nicotinic acid. This treatment program was used on these six patients and five achieved complete recovery.

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Involutional Schizophrenia

PEDRO POLONIO, M.D.
Lisbon, Portugal

The onset of schizophrenia after the age of 40 has been debated since the time of Kraepelin who found 5.8 per cent, and Mayer, who, working over the same material, found an incidence of 15 per cent. The disputed cases were those that Kraepelin tried to isolate under the term paraphrenia, but which Mayer identified as the same basic process. Such a view often raises interesting questions concerning the physiologic and psychologic changes in this period of life in the development and course of schizophrenia, as well as the relationships between schizophrenia and other psychoses formerly diagnosed as involutional.

In this study we have accepted M. Bleuler's criteria for the diagnosis of late or involutional schizophrenia:

1. Onset after the age of 40 years.
2. Symptomatology resembling schizophrenia.
3. Absence of memory defect or other sign of organic cerebral lesion.

In 492 patients with schizophrenia admitted to the hospital and followed for from five to ten years, we found 85 patients more than 40 years of age, 17 per cent. Females predominated to the extent of 55 per cent. Two thirds began between the ages of 40 and 50, and only three patients developed the disease at ages of 62, 65 and 67.

The only study of hereditary factors in involutional schizophrenia that we know of was made by M. Bleuler, and he reported no essential difference from typical schizophrenia. He also found instances where additional members of the family were experiencing symptoms similar to those found in the probands. Bleuler considered his material insufficient to draw conclusions beyond the probable identity of involutional schizophrenia with typical schizophrenia.

In the families of our cases we found the same incidence of "process" schizophrenia as in the controls, and a lesser frequency of periodicity in the earlier stages of the illness. Among the families of patients we found a somewhat higher incidence of other mental disorders such as epilepsy, senile dementia and mental deficiency, but without statistical significance.

Comparison of our figures with those of Bleuler shows that body build is somewhat different as indicated below:

	Bleuler	*Polonio*
Pyknic	49%	32%
Athletic	3%	15%
Asthenic	41%	52%
Mixed	3%	5%
TOTAL	100%	100%

The incidence of psychogenic factors was 23 per cent and of exogenous factors 24 per cent. Both these figures are more than double that of the control (typical schizophrenia) group, and have been advanced to explain some of the characteristics of involutional schizophrenia. Insidious onset was slightly more frequent, 68 per cent as against 62 per cent, while a stable personality was present in the prepsychotic period in 44 per cent as against 40 per cent.

In agreement with Bleuler, we found the symptomatology and course of involutional schizophrenia similar to other schizophrenias in nearly half of our cases. The final deterioration was not so marked. Spontaneous recovery occurred in 37 per cent as compared with 45 per cent for the whole control group, and 30 per cent for the group with onset at age 35-40. In the other half of our cases the onset of the disorder resembled that of the usual involutional psychosis. Those first diagnosed paraphrenia (21%) evolved into paranoid schizophrenia. A depressive syndrome with paranoid features occurred in 11 per cent. One of these patients was a 43 year old woman of pyknic build, depressed and anxious, with marked rigidity, who made a full recovery after elec-

From the Psychiatric Clinic of the University of Lisbon, Professor Barahona Fernandes, Director.

troshock therapy. The question of diagnosis between schizophrenia and manic-depressive psychosis was resolved by the development of typical schizophrenia in her son. Another patient was a 50 year old man of pyknic build who, after a period of intense work followed by failure in business, developed anxiety, depression, refusal of food, jealousy and delusion of poisoning. He recovered under insulin therapy, but the diagnosis of involutional schizophrenia was confirmed by the occurrence of schizophrenia in a sister and two cousins.

In cases like this the differential diagnosis between atypical depression and involutional schizophrenia may be difficult without confirmation either on the basis of hereditary factors, or subsequent course.

Seven patients began with symptoms of exogenous character; three were alcoholics whose schizophrenic signs developed after clearing of the toxic manifestations; six others conformed to the diagnosis of paranoia and two others experienced delusions of reference. Nearly three fourths of all patients with involutional schizophrenia show predominance of paranoid symptoms while catatonic symptoms develop in about 20 per cent and hebephrenic symptoms in 10 per cent. In this period of life, hebephrenia is somewhat different, manifesting itself mostly by affective indifference, lack of ethical feelings and bizarre behavior. Among the catatonics we have included a patient whose behavior resembled the rigid involutional depression of Medow, but who in the later course took on typical catatonic features. There were also two cases of acute catatonia developing after the age of 40 years (late catatonia of Jacobi) and rapidly progressing to death. Periodic course was rare.

Involutional schizophrenia responds to insulin treatment or to combined insulin treatment. Recoveries rose from 37 per cent to 62 per cent in this series. Several good prognostic features are present in these patients of middle age, such as pyknic build, good personality and exogenous factors, counteracting the lesser defense capacity of the aging organism. Shock therapy seems to stimulate the resistance of the organism and permits full action of these features.
features.

Discussion

There are no marked differences between involutional schizophrenia and typical schizophrenia. Paranoid forms predominate over catatonic and hebephrenic forms, a feature noted in increasing degree in the third decade. Pyknic body build increases in late schizophrenia. Precipitating factors, both exogenous and endogenous, occur in almost half of the cases, indicating a greater stress factor and consequently higher resistance. Greater stability of the adult personality and the slower biologic evolution at this time of life offer greater resistance to the destructive action of schizophrenia; in consequence deterioration is not so marked. However, recovery is less likely because of fixation.

Masking of the schizophrenic process by atypical depression is more frequent in the involutional period; the process is milder and slower in its evolution. At earlier ages, schizophrenia may start as an atypical depression but evolves more rapidly into a full-blown schizophrenic process.

In this study the great majority of involutional paranoid psychoses admitted to the hospital were paranoid schizophrenias. Involutional paranoia is no different from the paranoia evolving into schizophrenia at earlier ages. Most of the patients suffer in fact from mild schizophrenia, but there are occasional instances of reactive paranoid syndromes, and also of atypical manic-depressive psychoses.

Summary

Involutional schizophrenia presents in half the cases the same features as ordinary schizophrenia. In the rest there are some deviations that can be attributed to several factors such as age, greater frequency of pyknic build, more stable personality and greater incidence of precipitating factors both exogenous and endogenous. Atypical onset is more frequent, particularly with depression and hallucinosis.

The majority of the hospitalized patients with involutional paranoid psychoses are certainly schizophrenics.

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Neurological and Neuropathological Conference

HAMILTON FORD, M.D., and K. M. EARLE, M.D., *Editors*
Galveston, Texas

Summary Case No. P.M. 9520

Patient is a 34 year old female admitted from the Emergency Room to the John Sealy Hospital on August 13, 1953. She was referred to the Diagnostic Clinic by her local physician.

At the time of admission she complained of intense generalized headaches, feeling feverish, having extreme weakness, inability to move her legs, and inability to void. The immediate difficulty began seven weeks before, although there is a history of night sweats for the preceding several years. Also, she is said to have had the "Flu" in the Spring and since has been coughing up a thick, hard, yellowish sputum. Additionally, she has experienced the sensation of tightness in her chest. Seven weeks ago she began having dull, aching frontal headaches and to feeling feverish. She tried to go on with her work as a cook in a cafe, but became too weak. She consulted her doctor who took an X-ray of her chest, made a diagnosis of pneumonia, and administered penicillin. The fever, headaches, and general malaise persisted and two weeks later she consulted a local clinic where she was diagnosed as having virus pneumonia, asthma, and anemia. Three weeks ago she began to have trouble with her vision in that it seemed that a "skin was coming up from the outer corner of each eye and gradually covering up her vision on that side." It seemed that only the outside of each eye was affected. Although her fever lessened with prescribed medicines, aspirin and frequent daily cool sponges, she finally became so weak that she stayed in bed except for going to the bathroom. Three days before admission she attempted to get out of bed, but her legs buckled under her. By the following morning the feet and legs were feeling numb and she found that toe movement was the only thing which remained. This progressed to a complete paralysis by the time she reached the Emergency Room. She developed urinary retention and fecal incontinence on the day of admission. During the preceding three days the headaches were increasing in intensity and the neck began to feel stiff and sore. There was no other pain. As an after thought, she stated she had not menstruated in three months and thought she was pregnant.

The past history was not particularly relevant. She attended school to the fifth grade and had worked chiefly as a cook and housemaid. She married at twenty-seven, but was later divorced. There were three living children and one recent miscarriage which occurred following an automobile accident in October, 1952. At that time she received some "twisting injury of her neck" which remained painful for two or three weeks thereafter. Her father died of an unknown cause. The mother is living and well. Very little was known about the health of her eight siblings. The patient had the usual childhood diseases and is said to have had a "touch of diabetes nine years ago."

Initial examination revealed a temperature of 104; pulse, 100; and respiration 28 per minute. Examination of her eyes showed normal pupillary reaction, normal extra-ocular movements, and the fundi were not remarkable. The rest of the E.N.T. examination was normal. The neck was definitely stiff and was painful on movement, especially flexion. The chest showed no intercostal action from the fifth rib down. Diaphragmatic action was intact and the upper intercostals were active. There was hyperresonance of the upper left chest anteriorly with bubbling rales and expiratory wheezes in this area. The right chest was essentially clear. On the neurological examination the patient showed a complete flaccid paralysis of the legs with loss of all sensation below the 7th thoracic segment. The upper extremities showed some slight increase in deep tendon reflexes. There were no abnormal reflexes. The rest of the physical examination was normal, including the pelvis examination.

Laboratory Examination: X-ray of the chest showed a large cavity in the apex of the left lung. Cervical, thoracic, and lumbosacral spine films, and skull films, were normal. Urinalysis and blood chemistry, including serum proteins, fasting blood sugar, N.P.N., CO_2, and chlorides, were normal. Kolmer and Kahn, negative. The blood count was not unusual except for 8,000 white count with 52% polys and 12 stab forms. Spinal fluid examination revealed a few red blood cells with 25 white cells, of which 84% were lymphocytes and 16% polys. Protein was 152 mgm.%, chlorides 463 mgm.%, sugar 49 mgm.%, Wasserman negative and the Lange was normal. Spinal fluid culture was negative, nor were organisms (including fungi and yeast) isolated in several subsequent spinal fluid studies. Repeated spinal fluid examination showed a white count which varied from 15 to 4 cells with the protein varying from 84 to 93 mgm.%. Spinal fluid sugars were in the neighborhood of 50 mgm.%. Guinea pig inoculation with spinal fluid and mouse passage for virus, were negative. Acid fast organisms were isolated from the first and all subsequent sputum studies.

Within the first few days after admission the paralysis ascended up to a level of about Cervical 4 in that she lost part of her diaphragmatic motion and had some weakness in the muscles of the left forearm and hand. She was placed in a respirator

From University of Texas-Medical Branch.

and later in a rocking bed. The temperature subsided to 101 degrees on the second day of admission and thereafter varied from 99 to 101.6 rectally, until a terminal rise of 105 on the day of her death.

She was given the usual supportive measures, including all of the vitamin supplements, dihydrostreptomycin, P.A.S., and isoniazid. In late August she received a course of BAL. A progressive anemia called for the first blood transfusion on Sept. 1. With the subsidance of her fever, her headaches diminished and her nutritional intake improved. During the first few weeks the patient regained some vision, especially in the right eye. In October it is reported that she again lost most of her sight, but there was a slight improvement in the early weeks of November. Tidal drainage and bladder irrigations were a continuing necessity. She developed severe decubitus ulcers (these were grafted by the plastic surgery department) this, in spite of the air mattress and rocking bed. Repeat X-rays revealed some improvement in the condition of the left chest. She continued to be able to take nourishment until the twenty-seventh of December when she lapsed into a coma, temperature rose to 105 rectally, and she expired on December 28, 1953.

Clinical Discussion

Dr. Hamilton Ford: The patient's age 34 is of some significance as it places her in an age range compatible with a common neurologic disease. A review of the clinical abstract makes it possible to develop the progress of the patient's illness into five stages, as far as time sequence is concerned. Stage I, is the history of night sweats for several years, which will appear more significant as the material develops. Stage 2, is that of coughing up a heavy sputum for the previous six months and would be equally pertinent in what seems to be her primary condition. Stage 3, is that of headaches for a period of seven weeks, which may or may not be related to the original pathology. At least, this signifies a new development. Stage 4, beginning three weeks ago with visual disturbance, now verifies signs of nervous system involvement. Stage 5, coming on three days before admission characterized by paralysis of the legs and sphincter disturbance, confirms this opinion.

In the fifth stage there is also a history of increasing headaches with stiffness of the neck and of feeling more feverish. Certainly, she was a very ill patient at the time of admission. The majority of the students made a diagnosis of tuberculous meningitis secondary to pulmonary tuberculosis. The next most common diagnosis was multiple sclerosis. The third was tumor of the brain or spinal cord, and the fourth, poliomyelitis, though I would not concur with the latter. The long history of night sweats, later coughing and expectoration, together with sensations of tightness in the chest, fever, and a diagnosis of pneumonia elsewhere, makes pulmonary tuberculosis likely. In spite of all of this, she attempted to continue her work as a cook, which is particularly bad in view of her chest disease history.

It appears that the exacerbation which brought her here started seven weeks before when she began to have fever and headaches. Even in the light of later developments, the headaches at that time do not necessarily mean that she had developed intracranial disease. It is well known that fever produces cerebral vasodilatation and distention to cause headache and this could have been a part of her systemic illness. The abstract indicates she was not benefited by the antibiotics given her for the chest condition. With symptoms persisting, and as people are prone to do, she went shopping elsewhere. The next clinic considered her chest condition as pneumonia but also made an additional diagnosis of asthma and anemia and treated her for them. The onset of visual difficulty leaves no doubt about the invasion of her nervous system. The visual symptom and her rather unusual way of describing it, i.e., "a skim which seems to be coming up from the outer corner of each eye" to gradually occlude her outside vision, points to involvement of a particular portion of the optic pathway. Persons who have lived on a farm in the days when animals drew the farm implements, have described this loss of vision "as though I had blinders on"; meaning that they could not see laterally. This loss of both temporal fields of vision indicates a chiasmal lesion which damages the crossing nasal fibers, a finding so often encountered in certain pituitary tumors.

She continued to worsen and three days before admission developed a paralysis, as well as disturbance in sensation, in the lower extremities. This means that some other portion of the nervous system is involved, either in the brain or in the cord, and it points to the presence of more than one le-

sion—a diffuse involvement of the nervous system. This evidence of diffuseness is perhaps verified by the severe urinary and fecal incontinence coming on the day of admission. Such pronounced incontinence is compatible with a lesion in the sphincter centers in the sacral area of the cord. Thus, we have optic chiasma, brain or upper spinal cord and low cord pathology.

The present history causes us to consider chest pathology and then a diffuse involvement of the nervous system. The increasing headaches, the development of stiffness of the neck, and more fever, all paralleling the increasing nervous system symptoms, would make anyone with common sense think of an inflammatory condition of the nervous system, probably secondary to whatever is in her chest. In addition to tuberculosis, one would have to consider fungi and yeast-like infections and even a chronic atelectasis with a superimposed pneumonia and metastatic abscesses to the nervous system.

Now let us turn to her past history to see how much that will help. I note the statement about pregnancy and perhaps pelvic inflammatory disease, but believe it is put in here only as a "Red Herring." The recent miscarriage could signify lues but later it will be noted that the Wasserman on the blood and spinal fluid are both negative. The twisting injury of the neck might have caused cervical disc disease, later disc protrusion, and local cervical cord compression, but this would not explain the headaches and the visual symptoms. Normal blood sugars eliminate diabetes and a diabetic myelopathy.

The initial physical examination revealed a seriously ill patient with a high fever and a definitely stiff neck pointing to meningeal irritation. The chest findings were those which would be expected from her history. There is a flaccid paralysis of the legs with a loss of sensation below the seventh thoracic segments about the trunk; i.e., the upper limits of the cord involvement at admission. These sensory findings indicate cord disease so that the paralysis is probably not due to involvement of the motor pathways in the brain. Pelvic examination was negative and excludes this region as a source of infection. Thus, the physical examination lends further support to our idea that we are dealing with a meningitis, probably secondary to the chest infection. On the other hand, we must not overlook the possibility of a primary chest neoplasm with metastasis to the nervous system.

From available laboratory studies it can definitely be concluded that she had pulmonary tuberculosis for there were acid fast organisms in all the sputum studies. Hence, we have that diagnosis clinched but it does not aid us in our search for the etiology of her nervous system disease. You will note that the first spinal fluid examination did have 25 white cells with 84 per cent lymphocytes, a decrease in chlorides and sugar, and an increase in protein. There is nothing said about pellicle formation. This is the spinal fluid picture of a tuberculous meningitis but the negative guinea pig innoculation and the patient's clinical course, forces us to eliminate tuberculous meningitis. The abstract shows that she improved clinically with subsidence of temperature and neck stiffness in the first few days, even before the Dihydrostreptomycin, PAS, and Isoniazid could have become effective.

Returning to her spinal fluid, subsequent cell counts were always quite low, though the protein varied from 84 to 93 mgms.%. There were signs of cord, and perhaps, nerve root involvement which, if put together with the moderately elevated protein, the low cell count, and the upper respiratory infection, gives a pronounced picture of Guillain-Barré syndrome. Her subsequent clinical course is not compatible with this condition. Even though systemically improved, the lesion ascended into the mid cervical region for there was a weakness in the muscles of the left forearm and hand, and impaired action of the diaphragm. This means it reached the level of at least, cervical four, five and six segments from which the phrenic arises. Seemingly, there was no further cord progression as she was removed from the respirator and got along in a rocking bed for the five months prior to her death. In spite of vigorous, supportive measures and the administration of drugs now used in the treatment of tuberculosis, there was no improvement in the neurologic picture except that the ophthalmologists found improved

visual fields during the early Fall months. There was again progression of visual loss toward the end. Whether or not this could be considered as a true remission is a moot question.

Inquiry has been made about the use of BAL. This was a very sick patient and I believe that it was used more or less emperically, hopefully, and prayerfully, with the thought that this might be some type of viral infection (later reports on the mouse passages for virus were negative) or some degenerative condition, though doubt that anyone suspected heavy metal poisoning. It is my understanding that the BAL forms a protective barrier about nerve cells which prevents them from being invaded by circulating toxins or from the heavy metals.

The nurses are to be commended for their nursing care. Patients with spinal cord lesions present a tremendous problem, both from the standpoint of skin protection and prevention of decubitus and the management of the bladder. I will not attempt an explanation for the cause of her death, though it seems to have occurred quite suddenly as her course had been fairly stationary until a few hours before death.

To summarize, I believe that we will find more than one lesion with the pathology scattered along the neuro-axis and in the cranial nerves and nerve roots. I will say that it is not tuberculosis unless she has scattered tuberculomas but without meningitis. It could be a vascular disease; such as, one of the collagen-like disorders, periarteritis, or lupus erythematosus. There are no signs of other organ involvement to go along with this surmise. It was noted that she was 34 years of age, which places her at a likely age for the occurrence of one of the demyelinizing disorders; such as, multiple sclerosis. There is also some improvement in her vision at one stage which would fit into the remission so characteristic of this disorder. Too, multiple sclerosis involves the nervous system diffusely and it has a chief predilection for the optic nerve. There may even be cells in the spinal fluid on some occasions. The etiology would seem to rest between a demyelinizing disease and some undiscovered inflammatory condition.

Pathological Diagnoses

1. Multiple sclerosis (neuromyelitis optica type).
2. Pulmonary tuberculosis, extensive, with cavitation (left upper lobe) and miliary spread to pleura and liver.
3. Tuberculous abscesses of kidneys and ureters with obstruction of left ureter.
4. Tuberculous cystitis.
5. Chronic salpingitis.
6. Emaciation and malnutrition.
7. Decubitus ulcers of sacrum, right hip, knees and ankles.
8. Pyelonephritis, left.

Pathological Report

Dr. K. M. Earle:

The body was that of an extremely emaciated colored woman weighing about 75 pounds and measuring 67 inches in length. She appeared about the recorded age of 34 years. Large decubitus ulcers were present over the sacrum, right hip, knees and ankles.

Each pleural cavity contained 600 cc. of clear, straw-colored fluid. Both apices were covered by dense fibrous adhesions with smaller adhesions scattered over both lobes of the left lung. The larynx, trachea and bronchi were not remarkable. The right lung weighs 410 gms; left 400 gms. The left lung was extensively involved by a dense fibrocaseous process. The lung appeared shrunken with a large cavity measuring 4 x 5 cm. in the apex. The right lung showed miliary tubercles in the upper lobe, but was otherwise aerated. The middle lobe was less aerated and extensively involved by small tubercles. The lower lobe was extensively involved, but less than the middle lobe.

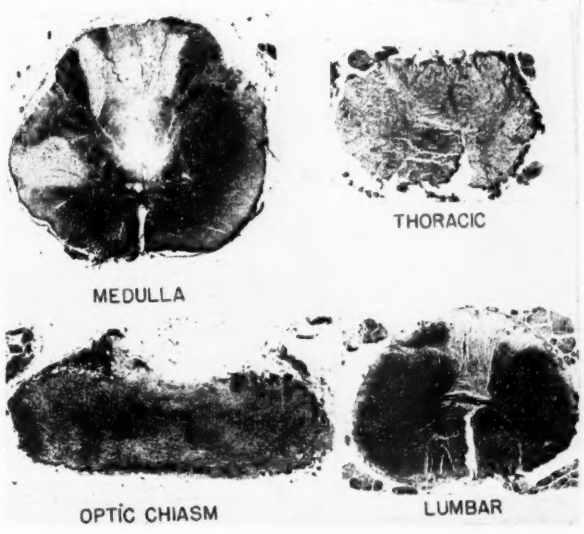

Fig. 1. Multiple Sclerosis ("neuromyelitis optic" or "optic neuromyelitis" type). Note white discoloration of optic chiasm and small white and gray plaques in the medulla and spinal cord. The section of thoracic cord shows almost complete demyelinization at this level.

The liver weighed 1290 grams, and it was light brown, firm and showed multiple small tubercles scattered within the parenchyma.

The kidneys weighed: R 160 gms., L 175 gms. Numerous tubercles could be seen beneath the capsule and on cut surface of both kidneys. Several large tuberculous abscesses were present in both kidneys. The left ureter was dilated in its upper portion due to partial obstruction, tuberculous involvement of the wall of the ureter.

Brain: weighed 1250 gms. On gross examination the cerebral hemispheres were pale and appeared moderately swollen. There was slight cloudiness of the leptomeninges, but no exudate. Coronal sections of the hemispheres revealed marked pallor of the optic chiasm, but no other specific lesions. Transverse sections of brainstem and cerebellum were not remarkable.

The spinal cord was markedly softened in the lower thoracic region. The leptomeninges over this area showed slightly milky opacity. Transverse sections of the cord showed marked softening with areas of white and gray discoloration of the thoracic cord for a distance of about 3 cm. Scattered areas of white and gray discoloration were found above and below the more extensive lesion of the thoracic cord. Small areas of gray discoloration could be seen in the lower medulla, but not in pons or midbrain.

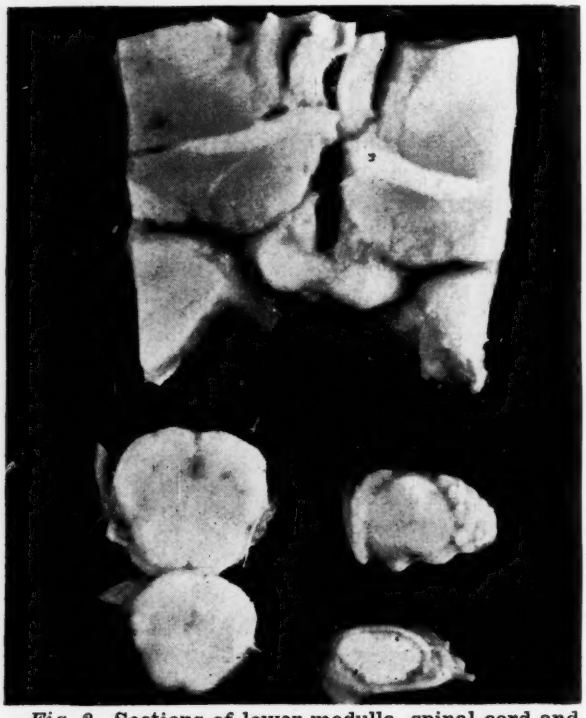

Fig. 2. Sections of lower medulla, spinal cord and optic chiasm showing plaques of multiple sclerosis with characteristic lack of ascending and descending degeneration. Note almost complete demyelinization of section of thoracic cord. Note patchy demyelinization of optic chiasm. Loyez stain.

Microscopically, section from the spinal cord and optic chiasm showed multiple areas of demyelinization with partial preservation of axis cylinders and astrocytic gliosis. These plaques were typical of the lesions of multiple sclerosis and varied considerably in age.

Comment

Dr. Kenneth Earle: This is a case of multiple sclerosis in a patient with extensive pulmonary tuberculosis. There seems to be no relationship between the two diseases and there was no evidence of tuberculous involvement of the central nervous system. Clinically and pathologically, the lesions in this case are typical of what has been described as "neuromyelitis optica." There is certainly a large area of demyelinization in the optic chiasm and multiple areas of demyelinization in the spinal cord. However, neuropathologists consider the lesions of "neuromyelitis optica" to be indistinguishable from the lesions of multiple sclerosis. The present tendency is to consider neuromyelitis optica as a type of multiple sclerosis which involves the optica chiasm and spinal cord predominantly.

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Pathologically, multiple sclerosis is characterized by a selective degeneration of myelin sheaths with preservation of most of the axis cylinders and reparative gliosis. The sparing of axis cylinders accounts for the fact that ascending and descending degeneration does not occur except in very old lesions. The lesions vary considerably in age and account for the clinical history of acute episodes (demyelinization and edema of surrounding tissue) followed by remissions (when the spared fibers begin to function again). The loss of fibers in the older lesions may be the result of disuse atrophy. The frequent location of plaques adjacent to the ventricles and reaching the surface of the spinal cord; the perivenous location of many plaques; and the close resemblance of the disease to post infective, post-vaccinal and experimental allergic encephalomyelitis have been the source of considerable research and speculation concerning etiology.

Although many theories have been proposed, the etiology of multiple sclerosis remains unknown.

CORRECTION

In the article, "Experimental Psychiatry III: A Chemical Concept of Psychosis," by Drs. Rinkel, Hyde and Solomon, September 1954 issue, page 262, the last paragraph, first sentence should read as follows:

"The obvious discrepancy in the result of our experiments with adrenochrome and that reported by Hoffer, Osmond and Smythies may have been primarily due to the difference in the molecule of the commercial product which is the semicarbazone of adrenochrome and furthermore seemed to find an explanation in their statement that the home-made adrenochrome solution they used was 'unstable' and 'deteriorating.'"

Noradrenalin in Anaphylactic Shock From Insulin

(Report of a Case)

WILLIAM D. BENHAM, M.D.
Washington, D. C.

In 1890, Koch demonstrated the phenomena of anaphylaxis but failed to recognize the significance of his observations with tuberculin preparations. The phenomena was reproduced by many researchers during the ensuing 12 years, but it was Charles Richet,[2] a French physiologist, who first grasped the significance of the phenomena in 1902. A pertinent extract of Richet's original description is as follows:

"The most typical experiment, that in which the result was indisputable, was carried out on a particularly healthy dog named "Neptune." He was given at first 0.1 cc. of the glycerin extract (tentacles of actinaria) without becoming ill; twenty-two days later, as he was in perfect health, I gave him a second injection of the same amount. In a few seconds he was extremely ill; breathing became difficult, and he was panting. He could scarcely drag himself along, lay on his side, was seized with diarrhea, vomited blood, sensibility diminished, and he died in twenty-five minutes."

It was Richet who gave the phenomena its name, anaphylaxis, which means "without protection." Considerable experimentation since that time has refined the description of symptomatology of anaphylactic reactions in both animals and man. Following a period of at least 10 to 15 days after the injection of a foreign protein, an injection of the same material (the most common experimental material is horse serum) is given. In anaphylactic shock reactions, there is a variable latent period from seconds to 30 minutes or even longer. The patient develops dyspnea, cyanosis, generalized and severe urticaria and erythema, edema of the tongue and throat, hacking cough, frothy expectoration, and circulatory collapse.

The case being reported is that of a 35 year old white woman who, while being treated for severe paranoid schizophrenia, developed an allergic sensitivity to insulin, went into anaphylactic shock, and was successfully treated with noradrenalin (Levophed).[3,4]

This patient was admitted to Walter Reed Army Hospital on December 13, 1953, five days after she became mentally ill as manifested by inappropriate speech, complete disregard for personal appearance, and frequent gesturing as if to an unseen conversant. On admission, the patient seemed much older than her stated 35 years, was unkempt, had delusions that she was to be a human sacrifice as a salvation for all mankind, had inappropriate affect and marked confusion in thought association. The patient had one previous hospitalization nine years earlier for a postpartum psychosis following the birth of the first of her three children. She was treated with electroconvulsive therapy and up to the present admission had apparently made a sufficiently satisfactory adjustment so that no further hospitalization was required.

The system review and the physical examination were noncontributory. The patient had always had good health and there was no history of any specific allergic disorder. Her blood pressure on admission was 120/80 and her pulse was 86. She was of sthenic body type with a tendency toward corpulence.

Electoconvulsive therapy was begun on December 18, 1953 and a total of 18 treatments were given all of which terminated with grand mal seizures. The last treatment was given on January 15, 1954. The patient showed no improvement during this course of therapy and it was decided to start her on insulin coma therapy. In testing for insulin sensitivity the patient was given five units of regular insulin before lunch on January 16, and 10 units on January 17. There was no untoward reaction. On January 18, 1954 she was started with 40 units of regular insulin with the intention of carrying her

From Department of Neuropsychiatry, Walter Reed Army Hospital, Washington 12, D.C.

into coma doses. Insulin treatment in this hospital is given five days a week, Monday through Friday. On January 29, the patient received 400 units of regular insulin in her ninth treatment with no comas up to that time. Her blood pressure had varied from 110/76 to 144/90 and her pulse from 72 to 120. There had been no local reactions at the site of the insulin injections, and no indication of any allergic reactions during the first nine insulin doses.

At 7:15 a.m. on February 1, 1954, the patient was given 400 units of regular insulin for her tenth treatment. From the time she received the insulin intramuscularly, she was under constant observation. At 7:45 it was noted that the patient's face was markedly flushed. Within five minutes she began to have edema of the face and lips. She was immediately given ½ cc. of 1:2600 adrenalin intramuscularly, and 60 cc. of 33 per cent glucose intravenously. At 7:55 she was given 150 mg. of pyribenzamine orally. Her blood pressure, which had been 118/76 had dropped to 80/40 at 8:00. The patient had a profuse diarrhea stool and urinated spontaneously at about 8:00. At 8:15 the blood pressure was 62/40 and the pulse was very weak, thready, and above 160. An infusion of 1000 cc. of 5 per cent glucose in normal saline was started at 8:20. At 8:25 the blood pressure was unobtainable, but the apical heart rate could be felt. At 8:30 4 cc. of a 1:1000 solution of noradrenalin was added to the infusion. At this time the patient was practically comatose. She vomited bile-stained material as well as the pyribenzamine she had been given earlier. The infusion was running at 60 drops per minute. At 8:40 the blood pressure was 96/70. It then rose steadily until at 9:10 it was 146/102 with the infusion running at 50 drops per minute. The infusion was then adjusted to maintain the systolic blood pressure at about 140 mm. Hg. At 9:50, the infusion stopped momentarily and the blood pressure fell to 80/40. The pulse rate continued at about 120. At 10:00 the patient was given 4 mg. of chlortrimeton intravenously with an additional 60 cc. of 33 per cent glucose. Periodically, the infusion was slowed to determine whether the patient could maintain her own blood pressure. By 10:50 only 20 drops per minute was required to maintain the blood pressure. At 11:00 the infusion was clamped off. The blood pressure first fell to 100/68 then slowly rose to 118/78 where it stabilized without noradrenalin. The patient was closely observed for the next 24 hours without incident.

It was noted by several observers that the patient's mental state seemed much improved during the time she was receiving the infusion of noradrenalin. During the prior weekend she had been almost in a catatonic state. Following the noradrenalin infusion she related well, was pleasant, socialized, and had an appropriate affect. This began about 15 minutes after the onset of the infusion and lasted for about three days, when she again manifested signs of an acute psychosis. Follow-up blood pressure and urine studies were within normal limits.

In the initial stages of the infusion the patient was receiving 4 micrograms of noradrenalin per minute. Over the course of two hours this was reduced to 1.3 micrograms per minute. In all she received 24 mg. of noradrenalin.

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